Better diagnostic tools needed to distinguish typhoid from other causes of acute febrile illness

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More than 8 million people contract typhoid annually, resulting in about 100 000 deaths. Despite associated sociopsychological and economic fallouts,[1] the typhoid diagnostics field has not accelerated sufficiently to allow reliable detection of this disease.[2] Co-occurrence of other acute undifferentiated febrile illnesses make clinical examination alone insufficient to differentiate typhoid from other such illnesses, making diagnostic evaluation essential.[3]

The most frequent co-endemic acute undifferentiated febrile illnesses are flaviviral illnesses, scrub typhus, malaria, leptospirosis and acute viral hepatitis.[3] Evaluations of diagnostics for typhoid and other acute undifferentiated febrile illnesses are complex. Despite the abundance of cases across the world, identifying one setting that allows studies to fulfil sample size requirements for more than one etiology is challenging. The reasons are diverse: pathogen occurrence is often seasonal, and diagnostic accuracy studies are rarely funded to last multiple seasons; and further reference testing can be extensive – to cover various etiologies. Therefore, evaluations are based on highly selected cohorts and do not reflect real-life scenarios from a clinical symptom or co-infection perspective. Various sources of biases are observed in acute undifferentiated febrile illnesses diagnostic test evaluations,[4] including comparisons with healthy controls only rather than those with similar febrile presentations; variable use of reference tests; and lack of reference samples to determine interlaboratory reproducibility. The result is a lack of representative studies that meet the standards of policy review committees, that could help advise on the appropriate use of diagnostic tests for acute undifferentiated febrile illnesses. The results of a recent study that assessed the performance of commercially available rapid typhoid diagnostic tests highlighted a lack of these tests.[5] The same study served as the basis of a data dossier submitted to the World Health Organization Strategic Advisory Group of Experts on in vitro diagnostics. The goal was to recommend against the use of these tests and prevent unnecessary use of typhoid rapid diagnostics in high-endemic settings.[6,7] The advisory group rejected this proposal, allowing continued use of these tests in endemic settings.[6] The main argument presented was the unavailability of alternative rapid tests, while acknowledging the suboptimal performance of currently available tests. Whether this decision will fuel further misuse of typhoid rapid diagnostics or provide momentum to typhoid diagnostic test development is debatable; however, the decision highlights a know-do gap in the medical community, where a suboptimal test is preferred to no test. This situation is unfortunate, especially as poor quality medical care can have detrimental outcomes to populations even if they have adequate health-care access.[8] Meanwhile, the gap in the generalizability of acute undifferentiated febrile illnesses diagnostics to populations of concern, and relevant guidance on algorithmic use of rapid typhoid diagnostic tests, remains unaddressed and needs attention.[9]

Several actionable insights emerge from these gaps that are relevant to future diagnostic test development and evaluations. First, investigators must aim to integrate clinical and laboratory results in diagnostic test evaluations. Clinicians are aware that the diagnosis of acute fever requires a combination of several clinical, physiological and contextual parameters. Systematic assessments of the discriminative power of various tests are important to determine the true added value of rapid tests. Second, researchers should use modelling approaches to identify algorithms worth evaluating in trial settings. Models can inform the incremental value and post-test probabilities of rapid diagnostic tests within clinical algorithms based on pretest accuracies of combinations of clinical signs. To improve testing algorithms for multiple pathogens, the global health community needs renewed data mining efforts to inform modelling approaches. Third, implementers should tailor diagnostic test interventions to the needs and preferences of end-users. Guidelines cannot be translated into interventions unless contextualized to specific practice settings. Qualitative studies should therefore be undertaken in high-burden settings to understand drivers of test use and physician-patient preferences to avoid translation failures. Fourth, funders should incentivize diagnostic research. As new infectious challenges emerge, it is important that funding focus does not shift away from this common cause of illness and death.

The recent World Health Assembly resolution on strengthening diagnostics capacity[10] is a reminder that diagnostic services are at the heart of surveillance, preparedness and optimal health outcomes. We hope that this call to action will motivate academia and industry to design, evaluate and implement fit-for-purpose tests for acute undifferentiated fever in the global market, to achieve sustainable health impacts. ■

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